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(54) Title: COMBINATION THERAPY FOR DEMENTIA, DEPRESSION AND APATHY

(57) Abstract: The invention provides compositions and kits for treating dementia, depression and apathy using combination therapies involving either a monoamine oxidase inhibitor or a selective serotonin reuptake inhibitor in combination with an anti-psychotic agent.

Combination Therapy for Dementia, Depression and Apathy

Field of the Invention

The invention is in the field of pharmaceutical therapies for psychiatric disorders such as apathy, dementia, or depression.

Background of the Invention

With increasing awareness of mental health issues and knowledge of the nervous system and neuropharmacology, progress has been made in the treatment of common psychiatric disorders, including dementia, depression, and apathy. There is however still a need for effective therapies that can stop, slow, reverse, or prevent the indications of dementia, depression, and apathy that accompany diverse mental disorders. There is also a need to refine and further characterise the diagnostic criteria that may be used to differentiate patients amenable to alternative therapeutic regimens.

Summary of Invention

The invention provides, in general, methods and compositions for treating psychiatric disorders, for example, apathy, dementia, or depression, using combination therapies such as a monoamine oxidase inhibitor or a selective serotonin reuptake inhibitor, in combination with an anti-psychotic agent.

In one aspect of the invention, there is provided, a method of treating dementia, depression, or apathy in a human subject, by administering a pharmaceutically effective amount of a monoamine oxidase inhibitor or a selective serotonin reuptake inhibitor, in combination with an anti-psychotic agent to the subject. The subject may for example have been diagnosed as being in need of such treatment in accordance with generally accepted clinical criteria, or criteria as disclosed herein.

In an alternative aspect of the invention, there is provided the use of a pharmaceutically effective amount of a monoamine oxidase inhibitor or a selective serotonin reuptake inhibitor in combination with an anti-psychotic agent for the preparation of a medicament for treating dementia, depression, or apathy.

In an alternative aspect of the invention, there is provided a pharmaceutical composition for treating dementia, depression, or apathy, including a monoamine oxidase

inhibitor or a selective serotonin reuptake inhibitor in combination with an anti-psychotic agent. The pharmaceutical composition may also comprise a pharmaceutically acceptable carrier.

In an alternative aspect of the invention, there is provided a kit for treating dementia, depression, or apathy, including a monoamine oxidase inhibitor or a selective serotonin reuptake inhibitor in combination with an anti-psychotic agent.

In alternative embodiments, the monoamine oxidase inhibitor may be a reversible monoamine oxidase inhibitor, for example, a reversible monoamine oxidase-A inhibitor, such as moclobemide, brofaromine, befloxatone, or toloxatone; the selective serotonin reuptake inhibitor may be fluoxetine, citalopram, fluvoxamine, sertraline, or paroxetine; and the anti-psychotic agent may for example be an atypical anti-psychotic agent, for example, risperidone, olanzapine, zotepine, ziprasidone, quetiapine, sertindole, or clozapine. The monoamine oxidase inhibitor may for example be selected from the group: isocarboxazid; pargyline; selegiline; furazolidone; phenelzine; amiflamine; iproniazid; nialamide; tranylcypromine; octamoxin; phenoxypropazine; pivalyl benzhydrazine; iproclozide; iproniazide; bifemelane; prodipine; benmoxin; etryptamine; fenoxypropazine; mebanazine; pheniprazine; safrazine; hypericine; iproniazid phosphate; phenelzine sulphate; tranylcypromine sulphate; moclobemide; brofaromine; befloxatone; toloxatone; clorgyline; L 51. 641; L 54. 761; L 54. 832; LY 121. 768; cimoxatone; bazinaprine; BW-1370U87; E-2011; harmine; harmaline; RS-8359; T-794; MDL 72394; MDL 72392; sercloremine; esuprone; clorgyline hydrochloride; mixtures thereof; and pharmaceutically acceptable salts thereof. The selective serotonin reuptake inhibitor may for example be selected from the group: fluoxetine; citalopram; fluvoxamine; sertraline; paroxetine; escitalopram; femoxetine; ifoxetine; indeloxazine; binedaline; nefazodone; trazodone; etoperidone; milnacipran; venlafaxine; desvenlafaxine; citalopram hydrobromide; fluoxetine hydrochloride; fluvoxamine maleate; paroxetine hydrochloride; sertraline hydrochloride; mixtures thereof; and pharmaceutically acceptable salts thereof. The combination may be synergistically effective at reducing any of the indications of dementia, depression, or apathy.

The composition may include moclobemide at a daily dosage of about 150 mg to about 600 mg, and any one of risperidone at a daily dosage of about 0.625 mg to about 3 mg, olanzapine at a daily dosage of about 0.625 mg to about 10 mg, zotepine at a daily

dosage of about 12.5 mg to about 300 mg, ziprasidone at a daily dosage of about 1.00 mg to about 80 mg, quetiapine at a daily dosage of about 12.5 mg to about 800 mg, sertindole at a daily dosage of about 6.25 mg to about 450 mg or clozapine at a daily dosage of about 1.00 mg to about 900 mg, per day, respectively. Alternatively the composition may include venlafaxine at a daily dosage of about 37.5 mg to about 375 mg, and any one of risperidone at a daily dosage of about 0.625 mg to about 3 mg, olanzapine at a daily dosage of about 0.625 mg to about 10 mg, zotepine at a daily dosage of about 12.5 mg to about 300 mg, ziprasidone at a daily dosage of about 1.00 mg to about 80 mg, quetiapine at a daily dosage of about 12.5 mg to about 800 mg, sertindole at a daily dosage of about 6.25 mg to about 450 mg or clozapine at a daily dosage of about 1.00 mg to about 900 mg, per day, respectively.

A "pharmaceutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve a desired therapeutic or prophylactic result, such as reduction of any of the indications of dementia, depression, or apathy. A pharmaceutically effective amount of a combination of a monoamine oxidase inhibitor or a selective serotonin reuptake inhibitor and an anti-psychotic agent, according to the invention, may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the combination to elicit a desired response in the individual. Dosage regimens may be adjusted to provide the optimum therapeutic or prophylactic response. A pharmaceutically effective amount is also generally one in which any toxic or detrimental effects of the combination are outweighed by the therapeutically or prophylactically beneficial effects, although an assessment of benefit or detriment may vary according to the severity of the condition to be treated.

A "synergistically effective" combination of a monoamine oxidase inhibitor or a selective serotonin reuptake inhibitor with an anti-psychotic agent is characterised by the fact that the monoamine oxidase inhibitor or the selective serotonin reuptake inhibitor is administered in a pharmaceutically effective amount and the anti-psychotic agent is administered in a pharmaceutically effective amount also, and the therapeutic effect thereby achieved, such as a reduction of any of the indications of dementia, depression, or apathy, is greater than the sum of the therapeutic effect that would be achieved with the monoamine oxidase inhibitor or the selective serotonin reuptake inhibitor alone in the pharmaceutically effective amount plus the therapeutic effect that would be achieved with the anti-psychotic

agent alone in the pharmaceutically effective amount. For example, a synergistically effective combination of risperidone and moclobemide is a combination wherein the moclobemide is administered in a pharmaceutically effective amount and risperidone is administered in a pharmaceutically effective amount, and the therapeutic effect on the indications of dementia, depression, or apathy thereby achieved is greater than the sum of the inhibition that would be achieved with risperidone alone in the pharmaceutically effective amount plus the inhibition that would be achieved with moclobemide alone in the pharmaceutically effective amount. Similarly, a synergistically effective combination of olanzapine and venlafaxine is a combination wherein the venlafaxine is administered in a pharmaceutically effective amount and olanzapine is administered in a pharmaceutically effective amount, and the therapeutic effect on the indications of dementia, depression, or apathy thereby achieved is greater than the sum of the inhibition that would be achieved with olanzapine alone in the pharmaceutically effective amount plus the inhibition that would be achieved with venlafaxine alone in the pharmaceutically effective amount.

"Treating", "treatment" or "to treat" as used herein means the medical management of a subject, usually a human subject, with the intent that a cure, amelioration, or prevention of dementia, depression, or apathy will result. This term includes active treatment, that is, treatment directed specifically toward improvement of dementia, depression, or apathy, and also includes causal treatment, that is, treatment directed toward removal of dementia, depression, or apathy. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of dementia, depression, or apathy; preventive treatment, that is, treatment directed to prevention of dementia, depression, or apathy; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of dementia, depression, or apathy.

Detailed Description of the Invention

In general, the invention provides methods and compositions for treating dementia, depression, or apathy associated with diverse mental disorders. The compositions of the invention include a monoamine oxidase inhibitor (MAOI) or a selective serotonin reuptake inhibitor (SSRI) in combination with an anti-psychotic agent.

Treatment of dementia, depression, or apathy using the combination compositions of the invention is more effective, in some embodiments, than that achieved in the absence of treatment (i.e., without employing exogenous agents or therapeutics) or by treatment with a MAOI or SSRI alone, or an anti-psychotic agent alone, wherein the combination is administered in a "synergistically effective" amount. In some embodiments, the combination compositions of the invention are useful in treating forms of dementia, depression, or apathy that are refractory to treatment using other therapeutic approaches.

In some embodiments, certain combinations are excluded from use according to aspects of the invention. For example, in some embodiments, a SSRI in combination with an anti-psychotic agent may be excluded as a therapy or prophylaxis, according to the invention, for any one or more of the disorders of dementia, depression, or apathy. In other embodiments, a MAOI or a reversible inhibitor of monoamine oxidase A (RIMA), in combination with an antagonist or agonist of a 5-HT receptor, or an anti-psychotic agent, may be excluded, for example, for the treatment of depression. In other embodiments, a combination of phenelzine and zisperidone may be excluded for the treatment of depression. In other embodiments, a combination of moclobemide with an atypical anti-psychotic agent may be excluded from the treatment of depression.

Dementia

Dementia is a neurodegenerative disorder generally characterized as the loss of an individual's learning and cognitive abilities, and is usually accompanied by behavioral, psychological, and motor symptoms. A critical element of dementia is the deficiency in short- and long-term memory, associated with difficulties in abstract thought, faulty judgment, personality change, and other impairments of higher cortical function. These impairments are generally so severe that the patient cannot maintain normal social activities or relationships. Typically, the loss of cognitive skills and memory in dementia is slow, with mental deterioration taking place over years. Dementia is most common among the elderly, and is becoming more widespread as the populations of developing countries age.

Many different dementias have been enumerated. For example, cortical dementia, fronto-temporal dementia, Alzheimer's dementia, lewy body dementia, progressive dementia, vascular dementia, multi-infarct dementia, drug- or alcohol-related dementia, and

Parkinson's-related dementia. Dementia may also result from head injury, cardiac arrest, radiation therapy for cancer, Acquired Immunodeficiency Syndrome (AIDS), Pick's disease, or Creutzfeldt-Jakob disease, including its variant form. Dementia is usually diagnosed according to its etiology, the two most common etiologies being Alzheimer's dementia and vascular dementia, for example, following stroke, in the elderly. Dementia is usually progressive and irreversible unless the etiology itself is treatable. Many patients have more than one type of dementia. A diagnosis of dementia generally involves ruling out major depressive disorder or delirium.

In most dementias, patients often exhibit primary cognitive symptoms as well as secondary behavioral symptoms. Cognitive symptoms may include things such as loss of memory, orientation perception, language and impaired judgement. Secondary or behavioral symptoms may include such things as personality and behavioral changes where the patient is aggressive or verbally agitated. Patients with dementia are often treated with anti-psychotic agents, benzodiazepines, beta-blockers, SSRIs, anti-depressants, anti-convulsives, and dietary supplements with limited efficacy.

Depression

Depression or depressive disorders generally manifest as feelings of intense sadness and despair that are not attributable to other causes, such as bereavement. Depressed patients may experience mental slowness and a loss of concentration, insomnia or hypersomnia, anorexia or weight gain, decreased energy and libido and disruption of normal circadian rhythms, body temperature and endocrine functions. The most common types of depression include unipolar or major depression, dysthymia, and bipolar disorder, which differ in the number of symptoms, severity, and persistence.

"Unipolar depression" or "major depression" generally means a clinical course where an individual experiences a period of at least two weeks during which there is either depressed or irritable mood or a marked loss of interest or pleasure in almost all activities. In children and adolescents, the mood may more generally be irritable rather than sad. The individual also experiences at least four additional symptoms drawn from a list that includes significant changes in appetite or weight (e.g., a change of more than 5% of body weight in a month), sleep, and psychomotor activity; fatigue or loss of energy; feelings of worthlessness or inappropriate guilt (which may be delusional); difficulty thinking,

concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation, plans, or attempts. Each symptom must be newly present or must have clearly worsened compared with the person's pre-episode status. The symptoms must persist for most of the day, nearly every day, for at least two consecutive weeks, and the episode must be accompanied by clinically significant distress or impairment in social, occupational (or academic), or other important areas of functioning. The episode may be a single episode or may be recurrent.

Major depression is thus characterized by one or more major depressive episodes in an individual without a history of manic, mixed, or hypomanic episodes. The diagnosis of unipolar or major depression is not made if: manic, mixed, or hypomanic episodes develop during the course of depression; if the depression is due to the direct physiological effects of a substance; if the depression is due to the direct physiological effects of a general medical condition; if the depression is due to a bereavement or other significant loss ("reactive depression"); or if the episodes are better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder. If manic, mixed, or hypomanic episodes develop, then the diagnosis is changed to a bipolar disorder.

"Dysthymia" is a less severe form of depression that involves a chronic malaise and exhibits many of the symptoms of major depression, but is not as disabling as is major depression. Dysthymia prevents an individual from functioning at his or her optimum level and is a long-term, low-grade disorder. An individual with dysthymia is likely to have at least one major depressive episode at some point. Thus, "dysthymia" or "dysthymic disorder" generally means a chronically depressed mood that occurs for most of the day, more days than not, for at least two years. In children and adolescents, the mood may be irritable rather than depressed, and the required minimum duration is one year. During the two year period (one year for children or adolescents), any symptom-free intervals last no longer than 2 months. During periods of depressed mood, at least two of the following additional symptoms are present: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty making decisions, and feelings of hopelessness. The symptoms may cause clinically significant distress or impairment in social, occupational (or academic), or other important areas of functioning. The diagnosis of dysthymia is not made if: the individual has ever had a manic episode, a

mixed episode, a hypomanic episode; has ever met the criteria for a cyclothymic disorder; the depressive symptoms occur exclusively during the course of a chronic psychotic disorder (e.g., schizophrenia); or if the disturbance is due to the direct physiological effects of a substance or a general medical condition. After the initial two-years of dysthymic disorder, major depressive episodes may be superimposed on the dysthymic disorder ("double depression").

"Bipolar disorder," also known as manic-depression, is characterized by severe mood swings, from high (mania) to low (depression). The mood swings may be abrupt or gradual. During the lows, an individual with bipolar disorder generally exhibits one or more of the symptoms of a depressive disorder.

Depression is often co-morbid with chronic general medical conditions, for example, cancer, diabetes, heart disease, stroke, HIV/AIDS, Parkinson's disease, particularly in the elderly. Empirically, women are more likely to suffer from a form of depression than men. In addition to psychotherapy and electroconvulsive therapy, patients with a form of depression are often treated with tricyclic anti-depressants (TCAs), MAOIs, SSRIs, and psychotropic drugs.

Apathy

Apathy is generally a behavioral disorder that is related to, but can be differentiated from, depression. Apathy is often defined as a lack of motivation not attributable to cognitive impairment, emotional distress, or decreased consciousness. Patients with apathy often have slowness of thinking and a decrease in their ability to refocus their thinking to accommodate a new topic. In addition, apathy is not a general decrease in cognitive function, but is rather associated with specific areas of cognitive dysfunction (Andersson S and AM Bergedalen, J Nerv Ment Dis 182:235-9, 1994; Kuzis et al. Neurology 52:1403-7, 1999).

Apathy refers to a syndrome closely related to major depression in that apathy is characterized by a lack of feeling or emotion or indifference. However, Apathy may be distinguished from major depression by the absence of depressed mood.

Apathy may also be of two types:

1. The inability to generate the feelings; and
2. The inability to motivate the self to experience the feelings.

Apathy may manifest during the course of unrelated neuropsychiatric disorders such as schizophrenia, Parkinson's Disease, Alzheimer's Disease, Multiple Sclerosis, Huntington's Disease, HIV/AIDS, stroke, head injury, myotonic dystrophy, cerebrovascular lesions, and frontal lobe lesions. Diagnosing apathy in a patient requires that abulia, akinesia, akinetic mutism, depression, dementia, delirium, despair, and demoralization first be ruled out.

Individuals diagnosed with apathy have been treated with agents such as methylphenidate, pemoline, dextroamphetamine, amantadine, amphetamine, bromocriptine, bupropion, or selegiline.

Diagnosis

The Diagnostic and Statistical Manual of Mental Disorders IV-TR, Fourth Edition, Text Revision, Washington, American Psychiatric Association, 2000 ("DSM-IV-TR") is commonly used among practitioners for diagnosing and treating mental disorders. An alternative standard for diagnosing mental disorders is provided by the tenth revision of the International Statistical Classification of Diseases and Related Health Problems ("ICD-10") under the aegis of the WHO. The ICD criteria are perhaps more prevalent in Europe than in North America, although the DSM-IV-TR is used extensively internationally. The National Institute for Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) also maintains a standard for diagnosis of mental disorders. With respect to the diagnosis of apathy, various measures are used, including the Apathy Inventory (Robert, PH et al., 2002, Int J Geriatr Psychiatry 17:1099-105), the Apathy Evaluation Scale (Marin, RS, 1996, Seminars Clin Neuropsychiatry.; 1: 304-314), and the Apathy Scale of Glenn et al. (Glenn MB et al., 2002, Brain Injury 16: 509-516). Diagnoses of dementia, depression, or apathy according to the invention may be performed using criteria established by the DSM-IV-TR, ICD-10, NINDS-AIREN, the different apathy scales, or any other standard accepted by mental health practitioners. Diagnoses of dementia, depression, or apathy according to the invention may also be performed using newly established or experimental criteria.

In some embodiments for diagnosis of a subject in need of treatment in accordance with the invention, Apathy may be defined as a syndrome closely related to major

depression in that apathy is characterized by a lack of feeling or emotion, or indifference. However, Apathy may be distinguished from major depression by the absence of depressed mood.

In some embodiments Apathy may also be considered as being of two types:

1. The inability to generate the feelings; and
2. The inability to motivate the self to experience the feelings.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors or MAOIs are a chemically heterogeneous class of anti-depressants that inhibit or affect the activity of monoamine oxidase in the brain, slowing the breakdown of monoamine neurotransmitters, thus affecting mood. Some non-selective MAO inhibitors have severe side effects, including adverse food and drug interactions. Some example of MAOIs include, but are not limited to the following:

isocarboxazid (Marplan® (Oxford Pharm.); CAS # 59-63-2);
pargyline (N-Methyl-N-propargylbenzylamine; CAS # 555-57-7);
selegiline (Elderpryl® (Somerset); CAS # 14611-51-9);
furazolidone (CAS # 67-45-8);
phenelzine (Nardil® (Pfizer); CAS # 51-71-8);
amiflamine ((+/-)-4-dimethylamino-a, 2-dimethylphenethylamine; Astra; CAS # 77518-07-1);
iproniazid (isonicotinic acid-2-isopropylhydrazide; CAS # 54-92-2);
nialamide (N-[2-(benzylcarbamoyl)ethyl]-N'-isonicotinyl hydrazide; CAS # 51-12-7);
tranylcypromine (Parnate® (GlaxoSmithKline); CAS # 155-09-9);
octamoxin (1-methylheptyl-hydrazine; CAS # 4687-87-1);
phenoxypropazine (Drazine®);
pivalyl benzhydrazine;
iproclozide (N'-(p-chlorophenoxyacetyl)-N'-isopropylhydrazine; CAS # 3544-35-2);
iproniazide (N-isonicotinyl-N'-isopropylhydrazine; CAS # 54-92-2);
bifemelane (4-(o-benzylphenoxy)-N-methylbutylamine (hydrochloride); CAS # 90293-01-9);
prodipine (1-(1-methylethyl)-4, 4-diphenylpiperidine or 1-isopropyl-4, 4-diphenylpiperidine; CAS # 31314-38-2);

benmoxin (N'-(a-methylbenzyl)benzohydrazine; CAS # 7654-03-7);

etryptamine (a-ethyl-1H-indole-ethanamine ;CAS # 2235-90-7);

fenoxypropazine (1-methyl-2-phenoxyethyl)hydrazine; CAS # 3818-37-9);

mebanazine (CAS # 65-64-5);

pheniprazine (a-methylphenethyl-hydrazine (hydrochloride); CAS # 55-52-7);

safrazine (1-methyl-3-(3, 4-methylenedioxyphenyl) propylhydrazine);

hypericine (1, 3, 4, 6, 8, 13-hexahydro-10.11-dimethyl-phenathro[1, 10.9, 8] perylen-7, 14-dione; CAS # 548-04-9); and

pharmaceutically acceptable salts thereof (for example iproniazid phosphate CAS # 305-33-9; phenelzine sulphate CAS # 156-51-4; and tranylcypromine sulphate CAS # 13492-01-8).

Selective MAO A inhibitors include, but are not limited to the following:

moclobemide (CAS # 71320-77-9);

brofaromine (CAS # 63638-91-5);

befloxatone (CAS # 134564-82-2);

toloxatone (CAS # 29218-27-7);

clorgyline (N-methyl-N-propargyl-3-(2, 4-dichlorophenoxy) propylamine; CAS # 17780-72-2);

L 51. 641 (Lilly) N-[2-(o-chlorophenoxy)ethyl] cyclopropylamine;

L 54. 761 (Lilly) phenacyl-cyclopropylamine;

L 54. 832 (Lilly) 2-naphthoylmethyl-cyclopropylamine;

LY 121. 768 (Lilly) N-[2-(o-iodophenoxy)ethyl] cyclopropylamine;

cimoxatone (3-[4-(5-methoxymethyl-2-oxo-oxazolidin-3-yl) phenoxymethyl] benzonitrile; CAS # 73815-11-9);

bazinaprine (3-[2-(morpholinoethyl)amino]-6-phenylpyridazine-4-carbonitrile; CAS # 94011-82-2);

BW-1370U87 (Burroughs Wellcome - 1-ethylphenoxathiin-10,10-dioxide);

E-2011 (Eisai - (5R)-3-[2-((1S)-3-cyano-1hydroxypropyl)benzothiazol- 6-yl]-5-methoxymethyl-2-oxazolidine);

harmine (7-methoxy-1-methyl-ß-carboline; CAS # 442-51-3);

harmaline (3, 4-dihydro-7-methoxy-1-methyl-ß-carboline; CAS # 304-21-2);

RS-8359 (Sankyo - (+/-)-4-(4-cyanoanilino)-5,6-dihydro-7-hydroxy-7H-cyclopenta[d]-py rimidine);

T-794 (Tanabe Seiyaku - [(5R)-3-(6-(cyclopropylmethoxy) 2-naphthalenyl)-5-(methoxymethyl) 2-oxazolidone]);

MDL 72394 (Marion Merrell - (E)-beta-Fluoromethylene-m-tyrosine);

MDL 72392 (Marion Merrell - (E)-beta-fluoromethylene-m-tyramine);

sercloremine (4-(5-chloro-2-benzofuranyl)-1-methylpiperidine (hydrochloride) Novartis - Ciba-Geigy);

esuprone (3, 4-dimethyl-2-oxo-2H-1-benzopyran-7-yl ethanesulfonate or 7-hydroxy-3, 4-dimethylcoumarin ethanesulfonate;(Knoll) CAS # 91406-11-0); and

pharmaceutically acceptable salts thereof (for example clorgyline hydrochloride CAS # 17780-75-5).

Some of the selective MAO A inhibitors listed above may have mixed MAO A and MAO B inhibitory activity, may be a bioprecursor which liberates an MAO A inhibitor when administered and may also be reversible MAO inhibitor.

Reversible inhibitors of monoamine oxidase Type A (RIMAs) are a sub-class of MAOIs that preferentially inhibit isoenzyme A of monamine oxidase and are reversible. RIMAs are considered safer and substantially more free of side effects, perhaps because isoenzyme B remains available to metabolize tyramine, which is present in some foods. RIMA anti-depressants include, but are not limited to, moclobemide, brofaromine, befloxatone (Bristol-Myers Squibb; (R)-5-(methoxymethyl)-3-(p[(R)-4, 4, 4-trifluoro-3-hydroxybutoxy]phenyl]-2-oxazolidinone; CAS # 134564-82-2) and toloxatone.

Moclobemide (Manerix® (Roche); p-chloro-N-(2-morpholinoethyl) benzamide; CAS # 71320-77-9) is an anti-depressant that affects the monoaminergic cerebral neurotransmitter system in a reversible manner. As a result of moclobemide treatment, patients generally have decreased metabolism of dopamine, norephinephrine and serotonin, therefore increasing the extracellular concentrations of these neurotransmitters. Moclobemide is often prescribed for major depression or in extreme cases of social phobia. US Patent No. 4,210,754 issued to Berkhard *et al.* (July 1, 1980), describes the compound moclobemide along with other related benzamides. Moclobemide's use in depression appears to have similar efficacy as that of TCAs, SSRIs, and non-selective irreversible MAOIs. However, moclobemide seems to have much fewer side effects than other anti-

depressant treatments, as well as fewer food and drug interactions. For these reasons, moclobemide has been widely used as an anti-depressant. Brofaromine (Consonar® (Novartis - Ciba-Geigy); 4-(5-methoxy-2 benzofuranyl)-piperidine; CAS # 63638-91-5) described in US Patent 4,210,655, and toloxatone (5-(hydroxymethyl)-3-m-tolyl-2-oxazolidinone; CAS # 29218-27-7), are RIMAs that are reported to have decreased extra-pyramidal effects, similar to moclobemide.

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors or SSRIs are antidepressant agents that increase the levels of serotonin (5-hydroxytryptamine or 5-HT) in the body by blocking the presynaptic serotonin transporter receptor. In some cases, SSRIs also affect the norepinephrine and/or the dopamine transporters, although to a lesser extent. Although SSRIs can have some side effects, including adverse food and drug interactions, in general they are considered more safe than older antidepressants and have been prescribed extensively. While SSRIs have been primarily prescribed for anxiety disorders and unipolar and bipolar major depression, their use in the treatment of other psychiatric conditions such as dysthymia, premenstrual syndrome, bulimia nervosa, obesity, obsessive compulsive disorder, borderline personality disorder, alcoholism, rheumatic pain, and migraine headache has been supported. Examples of SSRIs include, but are not limited to the following:

fluoxetine (Prozac®) (3-[(p-trifluoromethyl)phenoxy]-N-methyl-3-phenyl-propylamine (hydrochloride); CAS # 54910-89-3);

citalopram (Celexa®) (1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-1, 3-dihydro- isobenzofuran-5-carbonitrile; CAS # 59729-33-8);

fluvoxamine (Luvox®) ((E)-5-methoxy-4'-(trifluoromethyl)valerophenone O-(2-amino-ethyl)oxime (hydrogen maleate); CAS # 54739-18-3);

sertraline (Zoloft®) ((+)-cis(1S, 4S)-4-(3, 4-dichlorophenyl)-1, 2, 3, 4-tetrahydro-N-methyl-1-naphthylamine (HCl); CAS # 79617-96-2);

paroxetine (Paxil®) ((3S-trans)-3-[(1, 3-benzodioxol-5-yloxy) methyl]-4-(4-fluorophenyl)piperidine; CAS # 61869-08-7);

escitalopram (Cipralex®) ((S)-1-3-dimethylamino-propyl-1-(4'-fluoro-phenyl)-1,3-dihydro-isobenzofuran-5-carbonitril, oxalate);

femoxetine ((+)-trans-3-[(4-methoxyphenoxy)methyl]-N-methyl-4-phenyl piperidine; CAS # 59859-58-4);

ifoxetine ((+/-)-cis-4-(2, 3-xylyloxy)-3-piperidinol (sulfate); CAS # 66208-11-5);

indeloxazine ((+/-)-2-[(1H-inden-7-yloxy)methyl]morpholine hydrochloride; CAS # 60929-23-9);

binedaline (1-[[2-(dimethylamino)ethyl]methyl]amino-3-phenylindole; CAS # 60662-16-0);

nefazodone (1-[3-[4-(m-chlorophenyl)-1-piperazinyl]propyl]-3-ethyl-4-(2-phenoxyethyl)--^{2}-1, 2, 4-triazolin-5-one (HCl); CAS # 83366-66-9);

trazodone (2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-1, 2, 4-triazolo[4, 3-a]pyridin-3(2H)-one (hydrochloride); CAS # 19794-93-5);

etoperidone (1-[3-[4-(m-chlorophenyl)-1-piperazinyl] propyl]-3, 4-diethyl-Δ^{2}-1, 2, 4-triazolin-5-one (hydrochloride); CAS # 52942-31-1);

milnacipran ((+/-)-cis-2-aminomethyl-N, N-diethyl-1-phenylcyclopropane-carboxamide (hydrochloride) ;CAS # 92623-85-3);

venlafaxine (Effexor® Wyeth) (CAS # 93413-69-5);

desvenlafaxine (phenol, 4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]-(Z)-2-butanedioate (1:1) monohydrate)(*metabolite of venlafaxine*); and

pharmaceutically acceptable salts thereof (for example: citalopram hydrobromide CAS # 59729-32-7; fluoxetine hydrochloride CAS # 59333-67-4; fluvoxamine maleate CAS # 61718-82-9; paroxetine hydrochloride CAS # 78246-49-8; and sertraline hydrochloride 79559-97-0).

Anti-Psychotics

Anti-psychotic or neuroleptic agents are drugs that control agitated psychotic behavior, ameliorate disorders relating to thought and perception, and generally exert a calming effect. Atypical anti-psychotic or neuroleptic agents may be distinguished from "typical" anti-psychotic agents (for example, chlorpromazine or haloperidol) by their decreased extra-pyramidal side effects, especially dystonias.

Atypical anti-psychotics or atypical neuroleptics often include serotonin-2(5-HT2) and dopamine-2(D2) receptor antagonists. Examples of atypical anti-psychotics include, without limitation, 5-HT1A agonists (for example, ziprasidone: 5-[2-[4-(1,2-

benzoisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, described in U.S. Patent Nos. 4,831,031 and 5,312,925; quetiapine: 5-[2-(4-dibenzo[b, f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol, described in U.S. Patent No. 4,879,288), 5-HT1A antagonists (for example, risperidone: 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido-[1,2-a]pyrimidin-4-one, described in U.S. Patent No. 4,804,663; sertindole: 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-lH-indol-3-yl]-1-piperidinyl]ethyl]imidazolidin-2-one, described in U.S. Patent Nos. 4,710,500, 5,112,838, and 5,238,945), and α1-adrenoceptor antagonists (for example, clozapine: 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b, e][1,4]diazepine, described in U.S. Patent No. 3,539,573, and in Hanes, et al., 1988, Psychopharmacol. Bull. 24:62; olanzapine: 2-methyl-4-(4-methyl-1-piperazinyl)-lOH-thieno[2,3-b][1,5]benzodiazepine, described in U.S. Patent No. 5,229,382). Most have an affinity for the 5-HT2 receptor (for example, zotepine: 2-[(8-chlorodibenzo[b, f]thiepin-10-yl)oxy]-N,N-dimethylethylamine, described in British Patent 1,247,067, ziprasidone, quetiapine, sertindole, risperidone, and olanzapine).

Administration of atypical anti-psychotics or neuroleptics is recommended at the lowest possible dose consistent with a therapeutic response to reduce emerging extra-pyramidal symptoms, to minimize frequency and severity of side effects and toxicity. Patients may be routinely assessed for breast tenderness or galactorrhea, as an alternative clinical monitoring technique, for evidence of increasing serum levels of atypical neuroleptics.

Anti-psychotics, for example, atypical anti-psychotics, have been used for a variety of indications, including treatment of schizophrenia, manic episodes of bipolar disorder, agitation and psychotic symptoms of dementia, Tourette's Syndrome, and other disorders that manifest psychotic or agitated symptoms.

Compositions and Administration

Subjects having or at risk for apathy, dementia, or depression may be administered a pharmaceutically effective amount of a MAOI, RIMA, or SSRI in combination with an anti-psychotic agent, for example, an atypical anti-psychotic agent, or pharmaceutically acceptable derivatives or salts thereof, formulated in a pharmaceutically acceptable carrier or diluent. A "pharmaceutically acceptable carrier" or "excipient" includes any and all

solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. In some embodiments, supplementary active compounds can also be incorporated into the compositions.

A "pharmaceutically acceptable salt" includes salts of a MAOI, RIMA, SSRI, or anti-psychotic agent derived from the combination of any of these agents and an organic or inorganic acid or base. Such agents are useful in both non-ionized and salt form. In practice, the use of a salt form amounts to use of a base form; both forms are within the scope of the invention. As used herein, the term pharmaceutically acceptable salts or complexes refers to salts or complexes that retain the desired biological activity of the above-identified compounds and exhibit minimal undesired toxicological effects. Non-limiting examples of such salts are (a) acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid; (b) base addition salts formed with polyvalent metal cations such as zinc, calcium, bismuth, barium, magnesium, aluminum, copper, cobalt, nickel, cadmium, sodium, potassium, and the like, or with an organic cation formed from N,N-dibenzylethylene-diamine, D-glucosamine, ammonium, tetraethylammonium, or ethylenediamine; or (c) combinations of (a) and (b); e.g., a zinc tannate salt or the like.

Conventional pharmaceutical practice is employed to provide suitable formulations or compositions for administration to patients. Any appropriate route of administration may be employed, for example, oral, parenteral, sublingual, intravenous, subcutaneous, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, or aerosol administration. Methods well known in the art for making formulations are described, for example, in "Remington:

The Science and Practice of Pharmacy" (19th ed.) ed. A. R. Gennaro, 1995, Mack Publishing Company, Easton, PA, USA. The active compound(s) can also be administered through a transdermal patch (see, for example, Brown L. and Langer R. - Transdermal Delivery of Drugs, Annual Review of Medicine, 39:221-229 (1988)).

Oral formulations generally include an inert diluent or an edible carrier. For oral administration, the active compound(s) may be incorporated with excipients and used, for example, in the form of tablets, troches, or capsules or liquids. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. Methods for encapsulating compositions (such as in a coating of hard gelatin) for oral administration are well known (see, for example, Baker, Richard, Controlled Release of Biological Active Agents, John Wiley and Sons, 1986).

Formulations for parenteral, intradermal, subcutaneous, or topical application may be in the form of liquid solutions or suspensions and may contain, for example, excipients, sterile water, saline, polyalkylene glycols such as polyethylene glycol, propylene glycol or other synthetic solvents, oils of vegetable origin, fixed oils, or hydrogenated napthalenes, glycerine; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of toxicity such as sodium chloride or dextrose. If administered intravenously, the carriers may be physiological saline or phosphate buffered saline (PBS). Intranasal formulations may be in the form of powders, nasal drops, or aerosols. Formulations for inhalation may contain excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or may be oily solutions for administration in the form of nasal drops, or as a gel.

If desired, slow release or extended release delivery systems may be utilized to protect the compound(s) against rapid elimination from the body. These include implants

and microencapsulated delivery systems. Biocompatible, biodegradable polymers, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds. Other potentially useful parenteral delivery systems include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes (see, for example, US patent No. 4,522,811).

The MAOI, RIMA, or SSRI may be administered in a separate formulation from the anti-psychotic agent, or atypical anti-psychotic agent, or may be administered in a single formulation. In some embodiments, a single formulation containing both drugs may be used to improve patient compliance. However, individual formulations of the drugs may facilitate individual dosage adjustments.

A preferred dosage range for pharmaceutically effective amounts of the compounds may be delivered to achieve peak plasma concentrations of any value between 0.1 nM-0.1M, 0.1 nM-0.05M, 0.05 nM-15μM, or 0.01 nM-1μM. The concentration of active compound in the drug composition will depend on absorption, distribution, inactivation, and excretion rates of the drug as well as other standard factors. Daily dosages of each of the active compound(s) may range from about 0.1 to about 5000 mg, or from about 0.5 to about 1000 mg, or 1 to 500 mg, or 10 to 100 mg. The compound may administered in any suitable unit dosage form of active ingredient. In some embodiments, the combination of the MAOI, RIMA, or SSRI and the anti-psychotic agent, or atypical anti-psychotic agent, will be at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% more effective in treating apathy, dementia, or depression, than any of the compounds alone.

It is to be noted that dosage values may vary with the severity of the condition to be alleviated. For any particular subject, specific dosage regimens may be adjusted over time according to the individual need and the professional judgement of the person administering or supervising the administration of the compositions. Dosage ranges set forth herein are exemplary only and do not limit the dosage ranges that may be selected by medical practitioners. The amount of active compound in the composition may vary according to factors such as the disease-state, age, sex, and weight of the individual. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, a single bolus may be administered, several divided doses may be administered over time or the dose may

be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It may be advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form, as used herein, refers to physically discrete units suited as unitary dosages for subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment in individuals. In general, the compound(s) are administered in a dosage sufficient to deliver to a patient a therapeutically or prophylactically effective amount without causing serious toxic effects, although in particularly severe disorders a certain amount of toxicity or side effects may be tolerated.

The methods, uses, pharmaceutical compositions and kits described herein for the treatment of apathy, dementia, or depression may utilize or comprise a combination of one or more monoamine oxidase inhibitors in combination with one or more atypical anti-psychotic agents. Alternatively, the methods, uses, pharmaceutical compositions and kits described herein for the treatment of apathy, dementia, or depression may utilize or comprise a combination of one or more selective serotonin reuptake inhibitors in combination with one or more atypical anti-psychotic agents. Furthermore, such compositions may be in separate formulations or may be administered in a single formulation. Also, it will be appreciated that active agents described herein as monoamine oxidase inhibitors, selective serotonin reuptake inhibitors and atypical anti-psychotic agents may take the form of a metabolite or a precursor, which when metabolised forms an active agent. Representative examples of single monoamine oxidase inhibitors or single selective serotonin reuptake inhibitors in combination with an atypical anti-psychotic agent are shown in TABLE 1 below.

TABLE 1

	monoamine oxidase inhibitor or a selective serotonin reuptake inhibitor	**atypical anti-psychotic agent**
1.	isocarboxazid	ziprasidone
2.	pargyline	ziprasidone

3.	selegiline	ziprasidone
4.	furazolidone	ziprasidone
5.	phenelzine	ziprasidone
6.	amiflamine	ziprasidone
7.	iproniazid	ziprasidone
8.	nialamide	ziprasidone
9.	tranylcypromine	ziprasidone
10.	octamoxin	ziprasidone
11.	phenoxypropazine	ziprasidone
12.	pivalyl benzhydrazine;	ziprasidone
13.	iproclozide	ziprasidone
14.	iproniazide	ziprasidone
15.	bifemelane	ziprasidone
16.	prodipine	ziprasidone
17.	benmoxin	ziprasidone
18.	etryptamine	ziprasidone
19.	fenoxypropazine	ziprasidone
20.	mebanazine	ziprasidone
21.	pheniprazine	ziprasidone
22.	safrazine	ziprasidone
23.	hypericine	ziprasidone
24.	iproniazid phosphate	ziprasidone
25.	phenelzine sulphate	ziprasidone
26.	tranylcypromine sulphate	ziprasidone
27.	moclobemide	ziprasidone
28.	brofaromine	ziprasidone
29.	befloxatone	ziprasidone
30.	toloxatone	ziprasidone
31.	clorgyline	ziprasidone
32.	L 51. 641	ziprasidone
33.	L 54. 761	ziprasidone
34.	L 54. 832	ziprasidone
35.	LY 121. 768	ziprasidone
36.	cimoxatone	ziprasidone
37.	bazinaprine	ziprasidone
38.	BW-1370U87	ziprasidone
39.	E-2011	ziprasidone
40.	harmine	ziprasidone
41.	harmaline	ziprasidone
42.	RS-8359	ziprasidone
43.	T-794	ziprasidone
44.	MDL 72394	ziprasidone
45.	MDL 72392	ziprasidone
46.	sercloremine	ziprasidone
47.	esuprone	ziprasidone
48.	clorgyline hydrochloride	ziprasidone
49.	fluoxetine	ziprasidone
50.	citalopram	ziprasidone
51.	fluvoxamine	ziprasidone
52.	sertraline	ziprasidone
53.	paroxetine	ziprasidone
54.	escitalopram	ziprasidone
55.	femoxetine	ziprasidone
56.	ifoxetine	ziprasidone
57.	indeloxazine	ziprasidone

58.	binedaline	ziprasidone
59.	nefazodone	ziprasidone
60.	trazodone	ziprasidone
61.	etoperidone	ziprasidone
62.	milnacipran	ziprasidone
63.	venlafaxine	ziprasidone
64.	desvenlafaxine	ziprasidone
65.	citalopram hydrobromide	ziprasidone
66.	fluoxetine hydrochloride	ziprasidone
67.	fluvoxamine maleate	ziprasidone
68.	paroxetine hydrochloride	ziprasidone
69.	sertraline hydrochloride	ziprasidone
70.	isocarboxazid	quetiapine
71.	pargyline	quetiapine
72.	selegiline	quetiapine
73.	furazolidone	quetiapine
74.	phenelzine	quetiapine
75.	amiflamine	quetiapine
76.	iproniazid	quetiapine
77.	nialamide	quetiapine
78.	tranylcypromine	quetiapine
79.	octamoxin	quetiapine
80.	phenoxypropazine	quetiapine
81.	pivalyl benzhydrazine;	quetiapine
82.	iproclozide	quetiapine
83.	iproniazide	quetiapine
84.	bifemelane	quetiapine
85.	prodipine	quetiapine
86.	benmoxin	quetiapine
87.	etryptamine	quetiapine
88.	fenoxypropazine	quetiapine
89.	mebanazine	quetiapine
90.	pheniprazine	quetiapine
91.	safrazine	quetiapine
92.	hypericine	quetiapine
93.	iproniazid phosphate	quetiapine
94.	phenelzine sulphate	quetiapine
95.	tranylcypromine sulphate	quetiapine
96.	moclobemide	quetiapine
97.	brofaromine	quetiapine
98.	befloxatone	quetiapine
99.	toloxatone	quetiapine
100.	clorgyline	quetiapine
101.	L 51. 641	quetiapine
102.	L 54. 761	quetiapine
103.	L 54. 832	quetiapine
104.	LY 121. 768	quetiapine
105.	cimoxatone	quetiapine
106.	bazinaprine	quetiapine
107.	BW-1370U87	quetiapine
108.	E-2011	quetiapine
109.	harmine	quetiapine
110.	harmaline	quetiapine
111.	RS-8359	quetiapine
112.	T-794	quetiapine

113.	MDL 72394	quetiapine
114.	MDL 72392	quetiapine
115.	sercloremine	quetiapine
116.	esuprone	quetiapine
117.	clorgyline hydrochloride	quetiapine
118.	fluoxetine	quetiapine
119.	citalopram	quetiapine
120.	fluvoxamine	quetiapine
121.	sertraline	quetiapine
122.	paroxetine	quetiapine
123.	escitalopram	quetiapine
124.	femoxetine	quetiapine
125.	ifoxetine	quetiapine
126.	indeloxazine	quetiapine
127.	binedaline	quetiapine
128.	nefazodone	quetiapine
129.	trazodone	quetiapine
130.	etoperidone	quetiapine
131.	milnacipran	quetiapine
132.	venlafaxine	quetiapine
133.	desvenlafaxine	quetiapine
134.	citalopram hydrobromide	quetiapine
135.	fluoxetine hydrochloride	quetiapine
136.	fluvoxamine maleate	quetiapine
137.	paroxetine hydrochloride	quetiapine
138.	sertraline hydrochloride	quetiapine
139.	isocarboxazid	risperidone
140.	pargyline	risperidone
141.	selegiline	risperidone
142.	furazolidone	risperidone
143.	phenelzine	risperidone
144.	amiflamine	risperidone
145.	iproniazid	risperidone
146.	nialamide	risperidone
147.	tranylcypromine	risperidone
148.	octamoxin	risperidone
149.	phenoxypropazine	risperidone
150.	pivalyl benzhydrazine;	risperidone
151.	iproclozide	risperidone
152.	iproniazide	risperidone
153.	bifemelane	risperidone
154.	prodipine	risperidone
155.	benmoxin	risperidone
156.	etryptamine	risperidone
157.	fenoxypropazine	risperidone
158.	mebanazine	risperidone
159.	pheniprazine	risperidone
160.	safrazine	risperidone
161.	hypericine	risperidone
162.	iproniazid phosphate	risperidone
163.	phenelzine sulphate	risperidone
164.	tranylcypromine sulphate	risperidone
165.	moclobemide	risperidone
166.	brofaromine	risperidone
167.	befloxatone	risperidone

168.	toloxatone	risperidone
169.	clorgyline	risperidone
170.	L 51. 641	risperidone
171.	L 54. 761	risperidone
172.	L 54. 832	risperidone
173.	LY 121. 768	risperidone
174.	cimoxatone	risperidone
175.	bazinaprine	risperidone
176.	BW-1370U87	risperidone
177.	E-2011	risperidone
178.	harmine	risperidone
179.	harmaline	risperidone
180.	RS-8359	risperidone
181.	T-794	risperidone
182.	MDL 72394	risperidone
183.	MDL 72392	risperidone
184.	sercloremine	risperidone
185.	esuprone	risperidone
186.	clorgyline hydrochloride	risperidone
187.	fluoxetine	risperidone
188.	citalopram	risperidone
189.	fluvoxamine	risperidone
190.	sertraline	risperidone
191.	paroxetine	risperidone
192.	escitalopram	risperidone
193.	femoxetine	risperidone
194.	ifoxetine	risperidone
195.	indeloxazine	risperidone
196.	binedaline	risperidone
197.	nefazodone	risperidone
198.	trazodone	risperidone
199.	etoperidone	risperidone
200.	milnacipran	risperidone
201.	venlafaxine	risperidone
202.	desvenlafaxine	risperidone
203.	citalopram hydrobromide	risperidone
204.	fluoxetine hydrochloride	risperidone
205.	fluvoxamine maleate	risperidone
206.	paroxetine hydrochloride	risperidone
207.	sertraline hydrochloride	risperidone
208.	isocarboxazid	sertindole
209.	pargyline	sertindole
210.	selegiline	sertindole
211.	furazolidone	sertindole
212.	phenelzine	sertindole
213.	amiflamine	sertindole
214.	iproniazid	sertindole
215.	nialamide	sertindole
216.	tranylcypromine	sertindole
217.	octamoxin	sertindole
218.	phenoxypropazine	sertindole
219.	pivalyl benzhydrazine;	sertindole
220.	iproclozide	sertindole
221.	iproniazide	sertindole
222.	bifemelane	sertindole

223.	prodipine	sertindole
224.	benmoxin	sertindole
225.	etryptamine	sertindole
226.	fenoxypropazine	sertindole
227.	mebanazine	sertindole
228.	pheniprazine	sertindole
229.	safrazine	sertindole
230.	hypericine	sertindole
231.	iproniazid phosphate	sertindole
232.	phenelzine sulphate	sertindole
233.	tranylcypromine sulphate	sertindole
234.	moclobemide	sertindole
235.	brofaromine	sertindole
236.	befloxatone	sertindole
237.	toloxatone	sertindole
238.	clorgyline	sertindole
239.	L 51. 641	sertindole
240.	L 54. 761	sertindole
241.	L 54. 832	sertindole
242.	LY 121. 768	sertindole
243.	cimoxatone	sertindole
244.	bazinaprine	sertindole
245.	BW-1370U87	sertindole
246.	E-2011	sertindole
247.	harmine	sertindole
248.	harmaline	sertindole
249.	RS-8359	sertindole
250.	T-794	sertindole
251.	MDL 72394	sertindole
252.	MDL 72392	sertindole
253.	sercloremine	sertindole
254.	esuprone	sertindole
255.	clorgyline hydrochloride	sertindole
256.	fluoxetine	sertindole
257.	citalopram	sertindole
258.	fluvoxamine	sertindole
259.	sertraline	sertindole
260.	paroxetine	sertindole
261.	escitalopram	sertindole
262.	femoxetine	sertindole
263.	ifoxetine	sertindole
264.	indeloxazine	sertindole
265.	binedaline	sertindole
266.	nefazodone	sertindole
267.	trazodone	sertindole
268.	etoperidone	sertindole
269.	milnacipran	sertindole
270.	venlafaxine	sertindole
271.	desvenlafaxine	sertindole
272.	citalopram hydrobromide	sertindole
273.	fluoxetine hydrochloride	sertindole
274.	fluvoxamine maleate	sertindole
275.	paroxetine hydrochloride	sertindole
276.	sertraline hydrochloride	sertindole
277.	isocarboxazid	clozapine

278.	pargyline	clozapine
279.	selegiline	clozapine
280.	furazolidone	clozapine
281.	phenelzine	clozapine
282.	amiflamine	clozapine
283.	iproniazid	clozapine
284.	nialamide	clozapine
285.	tranylcypromine	clozapine
286.	octamoxin	clozapine
287.	phenoxypropazine	clozapine
288.	pivalyl benzhydrazine;	clozapine
289.	iproclozide	clozapine
290.	iproniazide	clozapine
291.	bifemelane	clozapine
292.	prodipine	clozapine
293.	benmoxin	clozapine
294.	etryptamine	clozapine
295.	fenoxypropazine	clozapine
296.	mebanazine	clozapine
297.	pheniprazine	clozapine
298.	safrazine	clozapine
299.	hypericine	clozapine
300.	iproniazid phosphate	clozapine
301.	phenelzine sulphate	clozapine
302.	tranylcypromine sulphate	clozapine
303.	moclobemide	clozapine
304.	brofaromine	clozapine
305.	befloxatone	clozapine
306.	toloxatone	clozapine
307.	clorgyline	clozapine
308.	L 51. 641	clozapine
309.	L 54. 761	clozapine
310.	L 54. 832	clozapine
311.	LY 121. 768	clozapine
312.	cimoxatone	clozapine
313.	bazinaprine	clozapine
314.	BW-1370U87	clozapine
315.	E-2011	clozapine
316.	harmine	clozapine
317.	harmaline	clozapine
318.	RS-8359	clozapine
319.	T-794	clozapine
320.	MDL 72394	clozapine
321.	MDL 72392	clozapine
322.	sercloremine	clozapine
323.	esuprone	clozapine
324.	clorgyline hydrochloride	clozapine
325.	fluoxetine	clozapine
326.	citalopram	clozapine
327.	fluvoxamine	clozapine
328.	sertraline	clozapine
329.	paroxetine	clozapine
330.	escitalopram	clozapine
331.	femoxetine	clozapine
332.	ifoxetine	clozapine

333.	indeloxazine	clozapine
334.	binedaline	clozapine
335.	nefazodone	clozapine
336.	trazodone	clozapine
337.	etoperidone	clozapine
338.	milnacipran	clozapine
339.	venlafaxine	clozapine
340.	desvenlafaxine	clozapine
341.	citalopram hydrobromide	clozapine
342.	fluoxetine hydrochloride	clozapine
343.	fluvoxamine maleate	clozapine
344.	paroxetine hydrochloride	clozapine
345.	sertraline hydrochloride	clozapine
346.	isocarboxazid	zotepine
347.	pargyline	zotepine
348.	selegiline	zotepine
349.	furazolidone	zotepine
350.	phenelzine	zotepine
351.	amiflamine	zotepine
352.	iproniazid	zotepine
353.	nialamide	zotepine
354.	tranylcypromine	zotepine
355.	octamoxin	zotepine
356.	phenoxypropazine	zotepine
357.	pivalyl benzhydrazine;	zotepine
358.	iproclozide	zotepine
359.	iproniazide	zotepine
360.	bifemelane	zotepine
361.	prodipine	zotepine
362.	benmoxin	zotepine
363.	etryptamine	zotepine
364.	fenoxypropazine	zotepine
365.	mebanazine	zotepine
366.	pheniprazine	zotepine
367.	safrazine	zotepine
368.	hypericine	zotepine
369.	iproniazid phosphate	zotepine
370.	phenelzine sulphate	zotepine
371.	tranylcypromine sulphate	zotepine
372.	moclobemide	zotepine
373.	brofaromine	zotepine
374.	befloxatone	zotepine
375.	toloxatone	zotepine
376.	clorgyline	zotepine
377.	L 51. 641	zotepine
378.	L 54. 761	zotepine
379.	L 54. 832	zotepine
380.	LY 121. 768	zotepine
381.	cimoxatone	zotepine
382.	bazinaprine	zotepine
383.	BW-1370U87	zotepine
384.	E-2011	zotepine
385.	harmine	zotepine
386.	harmaline	zotepine
387.	RS-8359	zotepine

388.	T-794	zotepine
389.	MDL 72394	zotepine
390.	MDL 72392	zotepine
391.	sercloremine	zotepine
392.	esuprone	zotepine
393.	clorgyline hydrochloride	zotepine
394.	fluoxetine	zotepine
395.	citalopram	zotepine
396.	fluvoxamine	zotepine
397.	sertraline	zotepine
398.	paroxetine	zotepine
399.	escitalopram	zotepine
400.	femoxetine	zotepine
401.	ifoxetine	zotepine
402.	indeloxazine	zotepine
403.	binedaline	zotepine
404.	nefazodone	zotepine
405.	trazodone	zotepine
406.	etoperidone	zotepine
407.	milnacipran	zotepine
408.	venlafaxine	zotepine
409.	desvenlafaxine	zotepine
410.	citalopram hydrobromide	zotepine
411.	fluoxetine hydrochloride	zotepine
412.	fluvoxamine maleate	zotepine
413.	paroxetine hydrochloride	zotepine
414.	sertraline hydrochloride	zotepine
415.	isocarboxazid	olanzapine
416.	pargyline	olanzapine
417.	selegiline	olanzapine
418.	furazolidone	olanzapine
419.	phenelzine	olanzapine
420.	amiflamine	olanzapine
421.	iproniazid	olanzapine
422.	nialamide	olanzapine
423.	tranylcypromine	olanzapine
424.	octamoxin	olanzapine
425.	phenoxypropazine	olanzapine
426.	pivalyl benzhydrazine;	olanzapine
427.	iproclozide	olanzapine
428.	iproniazide	olanzapine
429.	bifemelane	olanzapine
430.	prodipine	olanzapine
431.	benmoxin	olanzapine
432.	etryptamine	olanzapine
433.	fenoxypropazine	olanzapine
434.	mebanazine	olanzapine
435.	pheniprazine	olanzapine
436.	safrazine	olanzapine
437.	hypericine	olanzapine
438.	iproniazid phosphate	olanzapine
439.	phenelzine sulphate	olanzapine
440.	tranylcypromine sulphate	olanzapine
441.	moclobemide	olanzapine
442.	brofaromine	olanzapine

443.	befloxatone	olanzapine
444.	toloxatone	olanzapine
445.	clorgyline	olanzapine
446.	L 51. 641	olanzapine
447.	L 54. 761	olanzapine
448.	L 54. 832	olanzapine
449.	LY 121. 768	olanzapine
450.	cimoxatone	olanzapine
451.	bazinaprine	olanzapine
452.	BW-1370U87	olanzapine
453.	E-2011	olanzapine
454.	harmine	olanzapine
455.	harmaline	olanzapine
456.	RS-8359	olanzapine
457.	T-794	olanzapine
458.	MDL 72394	olanzapine
459.	MDL 72392	olanzapine
460.	sercloremine	olanzapine
461.	esuprone	olanzapine
462.	clorgyline hydrochloride	olanzapine
463.	fluoxetine	olanzapine
464.	citalopram	olanzapine
465.	fluvoxamine	olanzapine
466.	sertraline	olanzapine
467.	paroxetine	olanzapine
468.	escitalopram	olanzapine
469.	femoxetine	olanzapine
470.	ifoxetine	olanzapine
471.	indeloxazine	olanzapine
472.	binedaline	olanzapine
473.	nefazodone	olanzapine
474.	trazodone	olanzapine
475.	etoperidone	olanzapine
476.	milnacipran	olanzapine
477.	venlafaxine	olanzapine
478.	desvenlafaxine	olanzapine
479.	citalopram hydrobromide	olanzapine
480.	fluoxetine hydrochloride	olanzapine
481.	fluvoxamine maleate	olanzapine
482.	paroxetine hydrochloride	olanzapine
483.	sertraline hydrochloride	olanzapine

Example 1A

A pharmaceutical composition is prepared by combining moclobemide with any one of risperidone, olanzapine, zotepine, ziprasidone, quetiapine, sertindole, or clozapine in a pharmaceutically acceptable carrier. The composition includes moclobemide at a daily dosage of about 75 mg to about 600 mg, and any one of risperidone at a daily dosage of about 0.25 mg to about 3 mg, olanzapine at a daily dosage of about 0.625 mg to about 10 mg, zotepine at a daily dosage of about 12.5 mg to about 300 mg, ziprasidone at a daily

dosage of about 1.00 mg to about 80 mg, quetiapine at a daily dosage of about 12.5 mg to about 800 mg, sertindole at a daily dosage of about 6.25 mg to about 450 mg or clozapine at a daily dosage of about 1.00 mg to about 900 mg, per day, respectively. The composition is administered to a patient for treating dementia, depression, or apathy.

Example 1B

A pharmaceutical composition is prepared by combining moclobemide with any one of risperidone, olanzapine, zotepine, ziprasidone, quetiapine, sertindole, or clozapine in a pharmaceutically acceptable carrier. The composition includes moclobemide at a daily dosage of about 150 mg to about 600 mg, and any one of risperidone at a daily dosage of about 0.625 mg to about 3 mg, olanzapine at a daily dosage of about 0.625 mg to about 10 mg, zotepine at a daily dosage of about 12.5 mg to about 300 mg, ziprasidone at a daily dosage of about 1.00 mg to about 80 mg, quetiapine at a daily dosage of about 12.5 mg to about 800 mg, sertindole at a daily dosage of about 6.25 mg to about 450 mg or clozapine at a daily dosage of about 1.00 mg to about 900 mg, per day, respectively. The composition is administered to a patient for treating dementia, depression, or apathy.

Example 2A

A pharmaceutical composition is prepared by combining venlafaxine with any one of risperidone, olanzapine, zotepine, ziprasidone, quetiapine, sertindole, or clozapine in a pharmaceutically acceptable carrier. The composition includes venlafaxine at a daily dosage of about 37.5 mg to about 375 mg, and any one of risperidone at a daily dosage of about 0.25 mg to about 3 mg, olanzapine at a daily dosage of about 0.625 mg to about 10 mg, zotepine at a daily dosage of about 12.5 mg to about 300 mg, ziprasidone at a daily dosage of about 1.00 mg to about 80 mg, quetiapine at a daily dosage of about 12.5 mg to about 800 mg, sertindole at a daily dosage of about 6.25 mg to about 450 mg or clozapine at a daily dosage of about 1.00 mg to about 900 mg, per day, respectively. The composition is administered to a patient for treating dementia, depression, or apathy. Alternatively, the composition is prepared with risperidone at a daily dosage of about 0.625 mg to about 3 mg.

Example 2B

A pharmaceutical composition is prepared by combining venlafaxine with any one of risperidone, olanzapine, zotepine, ziprasidone, quetiapine, sertindole, or clozapine in a pharmaceutically acceptable carrier. The composition includes venlafaxine at a daily dosage of about 37.5 mg to about 375 mg, and any one of risperidone at a daily dosage of about 0.625 mg to about 3 mg, olanzapine at a daily dosage of about 0.625 mg to about 10 mg, zotepine at a daily dosage of about 12.5 mg to about 300 mg, ziprasidone at a daily dosage of about 1.00 mg to about 80 mg, quetiapine at a daily dosage of about 12.5 mg to about 800 mg, sertindole at a daily dosage of about 6.25 mg to about 450 mg or clozapine at a daily dosage of about 1.00 mg to about 900 mg, per day, respectively. The composition is administered to a patient for treating dementia, depression, or apathy.

Example 3

A 44 year female Caucasian presented in referral for apathy. This individual gave 5 year history of behavioral change followed by occupational impairment, social withdrawal then frankly decreased complex attention. A diagnosis of frontotemporal dementia was made.

A treatment plan for apathy was made whereby low dose moclobemide was titrated against low dose risperidone, commenced approximately 6 months following the initial diagnosis. Subsequently (approximately 2 months later), improvement was independently documented.

A further independent evaluation was made approximately 1 year and 1 month after treatment began and improvement in her apathy was noted.

Approximately 5 months later risperidone was discontinued for pharmacokinetic limitations and olanzapine commenced. With changes in the dose of olanzapine, the apathy was again effectively treated. The patient continued her work developing an advocacy network for persons with dementia and traveling internationally. This precipitated an independent medical evaluation by her disability insurer, which substantiated her diagnosis and the treatment effect.

The combination therapy (moclobemide and risperidone or olanzapine) exhibited a clinical efficacy that appeared to be greater than the cumulative effect that would have been

expected if the patient had been treated with an equivalent amount of moclobemide alone or with an equivalent amount of risperidone or olanzapine alone.

Example 4

A 49 year female was diagnosed at a specialized clinic with early onset Alzheimer's disease in 2001. Donepezil 10 mg daily was commenced. The clinical picture was complicated by a degree of anxiety and depressed mood. The depressed mood responded to venlafaxine 150 mg daily. The anxiety improved by systematically addressing life course issues.

Independent reassessment in 2003 by the specialized clinic revealed a mild degree of further cognitive decline with good compensating skills compensating well for some deficits. Venlafaxine was tapered and discontinued for excessive sweating. Moclobemide was commenced in place of venlafaxine. Risperidone was eventually prescribed at 0.25 mg daily. Her performance in Instrumental Activities of Daily Living (IADL's) improved as did the breadth and sophistication of her social activities.

Subsequent independent re-assessment by a specialized clinic in 2004 revealed cognitive improvement compared with the 2003 assessment and improvement on some test items on the original 2001 diagnostic assessment.

The emergence of dystonia with risperidone was managed by discontinuing the risperidone and commencing quetiapine. The overall improvement in IADL's and social function continued.

Example 5

A 79 year old retired sailor developed Parkinson's disease more than 5 years before admission to hospital. After the onset of Parkinson's disease he developed decreased motivation and decreased interest. The severity of the apathy progressed to a near total lack of initiative. A trial of methylphenidate for apathy was unsuccessful. He was admitted to hospital with anxiety, severe apathy and constipation. He was unable to function at home leading to caregiver burn out.

Core symptoms of delirium were absent. A shuffling gait devoid of heel strike or toe push was observed. Arm swing was decreased. This gentleman described decreased motivation in face of clear enjoyment of family visits and the sunshine outside. His

capacity for projective pleasure was preserved. He was satisfied with his accomplishments over his life. He felt his quality of life was reduced by his lack initiative. Objective mood and affect were flat. Thought form was marked by latency but progressed logically to a goal oriented conclusion. Thought content was free of delusions or hallucinations. Language was mildly impaired with paraphasic errors noted. Remote memories were difficult to recall and approximately correct. His sense of humor and capacity for abstraction were preserved.

Wechsler Adult Intelligence Scale®—Third Edition (WAIS III) testing revealed mild impairment of attention, praxis, reasoning, memory, response latency and difficulty in self correcting. This was judged consistent with Parkinson's disease by the registered psychologist.

An occupational therapy assessment in hospital on day 2 revealed decreased grip strength compromising his ability to dress and decreased range of movement compromising bathing. He could walk four lengths of the hallway.

Moclobemide was commenced day 4 at 75 mg. daily, increased to 150 mg. daily on day 8 and decreased to 75 mg daily on day 11. Olanzapine was commenced day 8 at 1.25 mg daily and continued at that dose.

Day 8 to 11 demonstrated the absence of depression by every day life. He enjoyed watching the Superbowl. He came into a small financial windfall and developed several plans to spend the money. Increased energy and increased social interaction were observed. Increased spontaneous activity led to independence in Activities of Daily Living (ADL). His walking improved to 400 feet.

Day 15 to 17 revealed increased mobile facial expression. He was able to learn, retain and employ movement strategies to eliminate postural hypotension. He was fully independent with his morning routine prior to discharge. He was discharged home independent in ADL.

Example 6

A 75 year retired nurse lived independently in the community until 2 months prior to admission. A progressive and gradual reduction in social patterns was reported over the preceding two years. However, she traveled internationally during that time.

Over the two months prior to admission she became more forgetful, refused support services, further withdrew from the community and described herself as "depressed". She acquired a thrush infection, became dehydrated and lost a great deal of weight.

Family and personal psychiatric history was negative. Salient medical history included a remote mastectomy for breast cancer, three vessel coronary bypass, acid peptic disease and hypertension.

Admitting mental status examination revealed a cachexic female suffering anxiety and lacking pleasure in previously pleasurable activities. Initiative was absent. Objective mood was dysphoric and affect restricted. Decreased concentration was apparent. The MMSE was 28/28 in nonstandard administration. She was completely dependent for activities of daily living (ADL).

Moclobemide was commenced at 200 mg. daily on day 4, increased to 300 mg. daily and day 6 and continued at 300 mg. daily.

Risperidone was commenced at 0.5 mg daily on day 7, discontinued on day 14 then restarted at 0.5 mg daily alternating with 0.25 mg. daily and continued as such.

The first three days of the admission showed prominent depressed mood in the morning with very limited improvement in the late afternoon. The late afternoon quality of mood and mobility of affect improved by Day 6.

By Day 13 pleasure was experienced and her affect mobilized. She described herself as unable to cook, clean for care for herself prior to admission. With step by step instructions she could progress through her Activities of Daily Living (ADL). Shortly after, mild extrapyramidal symptoms emerged. Therefore, risperidone was decreased.

Self-toileting emerged on Day 16. By Day 20 she reported an euthymic mood and denied treatment emergent side effects. Examination showed some mobility of affect and normal muscle tone. However, she remained without initiative to commence and complete almost all ADL.

By Day 24 self initiation of ADL was consistently observed. From Day 28 forward both self initiation and self supervision of ADL to completion was consistently observed. She resumed her usual hobby of reading on Day 45. Her 3MS score on Day 45 was 80/100. She was discharged to an intermediate care facility where she continued regular activity. Eventually she took up square dancing and returned to international travel.

Other Embodiments

Although various embodiments of the invention are disclosed herein, many adaptations and modifications may be made within the scope of the invention in accordance with the common general knowledge of those skilled in this art. Such modifications include the substitution of known equivalents for any aspect of the invention in order to achieve the same result in substantially the same way. Numeric ranges are inclusive of the numbers defining the range. In the specification, the word "comprising" is used as an open-ended term, substantially equivalent to the phrase "including, but not limited to", and the word "comprises" has a corresponding meaning. Citation of references herein shall not be construed as an admission that such references are prior art to the present invention. The invention includes all embodiments and variations substantially as described herein.

What is claimed is:

1. A method of treating dementia, depression, or apathy in a human subject in need thereof, comprising administering a pharmaceutically effective amount of a monoamine oxidase inhibitor or a selective serotonin reuptake inhibitor in combination with an anti-psychotic agent to the subject.
2. The method according to claim 1, wherein the monoamine oxidase inhibitor is a reversible monoamine oxidase inhibitor.
3. The method according to claim 1 or 2, wherein the reversible monoamine oxidase inhibitor is a reversible monoamine oxidase-A inhibitor.
4. The method according to any one of claims 1 through 3, wherein the reversible monoamine oxidase inhibitor is selected from the group consisting of moclobemide, brofaromine, befloxatone, toloxatone, mixtures thereof, and pharmaceutically acceptable salts thereof.
5. The method according to claim 1, wherein the selective serotonin reuptake inhibitor is selected from the group consisting of fluoxetine, citalopram, fluvoxamine, sertraline, paroxetine, mixtures thereof, and pharmaceutically acceptable salts thereof.
6. The method according to any one of claims 1 through 5, wherein the anti-psychotic agent is an atypical anti-psychotic agent.
7. The method according to any one of claims 1 through 6, wherein the atypical anti-psychotic agent is selected from the group comprising risperidone, olanzapine, zotepine, ziprasidone, quetiapine, sertindole, clozapine, mixtures thereof, and pharmaceutically acceptable salts thereof.
8. Use of a pharmaceutically effective amount of a monoamine oxidase inhibitor or a selective serotonin reuptake inhibitor in combination with an anti-psychotic agent for the preparation of a medicament for treating dementia, depression, or apathy.
9. The use according to claim 8, wherein the monoamine oxidase inhibitor is a reversible monoamine oxidase inhibitor.
10. The use according to claim 8 or 9, wherein the reversible monoamine oxidase inhibitor is a reversible monoamine oxidase-A inhibitor.
11. The use according to any one of claims 8 through 10, wherein the reversible monoamine oxidase inhibitor is selected from the group consisting of moclobemide,

brofaromine, befloxatone, toloxatone, mixtures thereof, and pharmaceutically acceptable salts thereof.

12. The use according to claim 8, wherein the selective serotonin reuptake inhibitor is selected from the group consisting of fluoxetine, citalopram, fluvoxamine, sertraline, paroxetine, mixtures thereof, and pharmaceutically acceptable salts thereof.

13. The use according to any one of claims 8 through 12, wherein the anti-psychotic agent is an atypical anti-psychotic agent.

14. The use according to any one of claims 8 through 13, wherein the atypical anti-psychotic agent is selected from the group comprising risperidone, olanzapine, zotepine, ziprasidone, quetiapine, sertindole, clozapine, mixtures thereof, and pharmaceutically acceptable salts thereof.

15. A pharmaceutical composition for treating dementia, depression, or apathy, comprising a monoamine oxidase inhibitor or a selective serotonin reuptake inhibitor in combination with an anti-psychotic agent.

16. The composition according to claim 15, wherein the monoamine oxidase inhibitor is a reversible monoamine oxidase inhibitor.

17. The composition according to claim 15 or 16, wherein the reversible monoamine oxidase inhibitor is a reversible monoamine oxidase-A inhibitor.

18. The composition according to any one of claims 15 through 17, wherein the reversible monoamine oxidase inhibitor is selected from the group consisting of moclobemide, brofaromine, befloxatone, toloxatone, mixtures thereof, and pharmaceutically acceptable salts thereof.

19. The composition according to claim 15, wherein the selective serotonin reuptake inhibitor is selected from the group consisting of fluoxetine, citalopram, fluvoxamine, sertraline, paroxetine, mixtures thereof, and pharmaceutically acceptable salts thereof.

20. The composition according to any one of claims 15 through 19, wherein the anti-psychotic agent is an atypical anti-psychotic agent.

21. The composition according to any one of claims 15 through 20, wherein the atypical anti-psychotic agent is selected from the group comprising risperidone, olanzapine, zotepine, ziprasidone, quetiapine, sertindole, clozapine, mixtures thereof, and pharmaceutically acceptable salts thereof.

22. A kit for treating dementia, depression, or apathy, comprising a monoamine oxidase inhibitor or a selective serotonin reuptake inhibitor in combination with an anti-psychotic agent.

23. The kit according to claim 22, wherein the monoamine oxidase inhibitor is a reversible monoamine oxidase inhibitor.

24. The kit according to claim 22 or 23, wherein the reversible monoamine oxidase inhibitor is a reversible monoamine oxidase-A inhibitor.

25. The kit according to any one of claims 22 through 24, wherein the reversible monoamine oxidase inhibitor is selected from the group consisting of moclobemide, brofaromine, befloxatone, toloxatone, mixtures thereof, and pharmaceutically acceptable salts thereof.

26. The kit according to claim 22, wherein the selective serotonin reuptake inhibitor is selected from the group consisting of fluoxetine, citalopram, fluvoxamine, sertraline, paroxetine, mixtures thereof, and pharmaceutically acceptable salts thereof.

27. The kit according to any one of claims 22 through 26, wherein the anti-psychotic agent is an atypical anti-psychotic agent.

28. The kit according to any one of claims 22 through 27, wherein the atypical anti-psychotic agent is selected from the group comprising risperidone, olanzapine, zotepine, ziprasidone, quetiapine, sertindole, clozapine, mixtures thereof, and pharmaceutically acceptable salts thereof.

29. The method according to claim 1, wherein the monoamine oxidase inhibitor is selected from the group consisting of:

isocarboxazid; pargyline; selegiline; furazolidone; phenelzine; amiflamine; iproniazid; nialamide; tranylcypromine; octamoxin; phenoxypropazine; pivalyl benzhydrazine; iproclozide; iproniazide; bifemelane; prodipine; benmoxin; etryptamine; fenoxypropazine; mebanazine; pheniprazine; safrazine; hypericine; iproniazid phosphate; phenelzine sulphate; tranylcypromine sulphate; moclobemide; brofaromine; befloxatone; toloxatone; clorgyline; L 51. 641; L 54. 761; L 54. 832; LY 121. 768; cimoxatone; bazinaprine; BW-1370U87; E-2011; harmine; harmaline; RS-8359; T-794; MDL 72394; MDL 72392; sercloremine; esuprone; clorgyline hydrochloride; mixtures thereof; and pharmaceutically acceptable salts thereof;

and wherein the selective serotonin reuptake inhibitor is selected from the group consisting of:

fluoxetine; citalopram; fluvoxamine; sertraline; paroxetine; escitalopram; femoxetine; ifoxetine; indeloxazine; binedaline; nefazodone; trazodone; etoperidone; milnacipran; venlafaxine; desvenlafaxine; citalopram hydrobromide; fluoxetine hydrochloride; fluvoxamine maleate; paroxetine hydrochloride; sertraline hydrochloride; mixtures thereof; and pharmaceutically acceptable salts thereof.

30. The use according to claim 8, wherein the monoamine oxidase inhibitor is selected from the group consisting of:

isocarboxazid; pargyline; selegiline; furazolidone; phenelzine; amiflamine; iproniazid; nialamide; tranylcypromine; octamoxin; phenoxypropazine; pivalyl benzhydrazine; iproclozide; iproniazide; bifemelane; prodipine; benmoxin; etryptamine; fenoxypropazine; mebanazine; pheniprazine; safrazine; hypericine; iproniazid phosphate; phenelzine sulphate; tranylcypromine sulphate; moclobemide; brofaromine; befloxatone; toloxatone; clorgyline; L 51. 641; L 54. 761; L 54. 832; LY 121. 768; cimoxatone; bazinaprine; BW-1370U87; E-2011; harmine; harmaline; RS-8359; T-794; MDL 72394; MDL 72392; sercloremine; esuprone; clorgyline hydrochloride; mixtures thereof; and pharmaceutically acceptable salts thereof;

and wherein the selective serotonin reuptake inhibitor is selected from the group consisting of:

fluoxetine; citalopram; fluvoxamine; sertraline; paroxetine; escitalopram; femoxetine; ifoxetine; indeloxazine; binedaline; nefazodone; trazodone; etoperidone; milnacipran; venlafaxine; desvenlafaxine; citalopram hydrobromide; fluoxetine hydrochloride; fluvoxamine maleate; paroxetine hydrochloride; sertraline hydrochloride; mixtures thereof; and pharmaceutically acceptable salts thereof.

31. The pharmaceutical composition according to claim 15, wherein the monoamine oxidase inhibitor is selected from the group consisting of:

isocarboxazid; pargyline; selegiline; furazolidone; phenelzine; amiflamine; iproniazid; nialamide; tranylcypromine; octamoxin; phenoxypropazine; pivalyl

benzhydrazine; iproclozide; iproniazide; bifemelane; prodipine; benmoxin; etryptamine; fenoxypropazine; mebanazine; pheniprazine; safrazine; hypericine; iproniazid phosphate; phenelzine sulphate; tranylcypromine sulphate; moclobemide; brofaromine; befloxatone; toloxatone; clorgyline; L 51. 641; L 54. 761; L 54. 832; LY 121. 768; cimoxatone; bazinaprine; BW-1370U87; E-2011; harmine; harmaline; RS-8359; T-794; MDL 72394; MDL 72392; sercloremine; esuprone; clorgyline hydrochloride; mixtures thereof; and pharmaceutically acceptable salts thereof;

and wherein the selective serotonin reuptake inhibitor is selected from the group consisting of:

fluoxetine; citalopram; fluvoxamine; sertraline; paroxetine; escitalopram; femoxetine; ifoxetine; indeloxazine; binedaline; nefazodone; trazodone; etoperidone; milnacipran; venlafaxine; desvenlafaxine; citalopram hydrobromide; fluoxetine hydrochloride; fluvoxamine maleate; paroxetine hydrochloride; sertraline hydrochloride; mixtures thereof; and pharmaceutically acceptable salts thereof.

32. The kit according to claim 22, wherein the monoamine oxidase inhibitor is selected from the group consisting of:

isocarboxazid; pargyline; selegiline; furazolidone; phenelzine; amiflamine; iproniazid; nialamide; tranylcypromine; octamoxin; phenoxypropazine; pivalyl benzhydrazine; iproclozide; iproniazide; bifemelane; prodipine; benmoxin; etryptamine; fenoxypropazine; mebanazine; pheniprazine; safrazine; hypericine; iproniazid phosphate; phenelzine sulphate; tranylcypromine sulphate; moclobemide; brofaromine; befloxatone; toloxatone; clorgyline; L 51. 641; L 54. 761; L 54. 832; LY 121. 768; cimoxatone; bazinaprine; BW-1370U87; E-2011; harmine; harmaline; RS-8359; T-794; MDL 72394; MDL 72392; sercloremine; esuprone; clorgyline hydrochloride; mixtures thereof; and pharmaceutically acceptable salts thereof;

and wherein the selective serotonin reuptake inhibitor is selected from the group consisting of:

fluoxetine; citalopram; fluvoxamine; sertraline; paroxetine; escitalopram; femoxetine; ifoxetine; indeloxazine; binedaline; nefazodone; trazodone;

etoperidone; milnacipran; venlafaxine; desvenlafaxine; citalopram hydrobromide; fluoxetine hydrochloride; fluvoxamine maleate; paroxetine hydrochloride; sertraline hydrochloride; mixtures thereof; and pharmaceutically acceptable salts thereof.

33. The method according to claim 1, wherein the combination is synergistically effective.

34. The use according to claim 8, wherein the combination is synergistically effective.

35. The pharmaceutical composition according to claim 15, wherein the combination is synergistically effective.

36. The kit according to claim 22, wherein the wherein the combination is synergistically effective.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2004/002071

A. CLASSIFICATION OF SUBJECT MATTER
According to International Patent Classification (IPC) or to both national classification and IPC
IPC7: A61K-31/551, A61K-31/137, A61K-31/5375, A61K-31/519, A61P-25/24, A61P- 25/28

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

Canadian Patent Database, United States Patent Database, Espacenet, Delphion, PubMed, Medscape, Google Keywords Monoamine oxidase inhibitor and related terms, antipsychotic and related terms, dementia, Alzheimer, Augmentation, Combination, Synergy

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No(s).
X	CA 2364211 (Chappell et al.) 2002-06-05 (see page 2, lines 30-36, page 5 and page 38, lines 27-36)	1-4, 6-11, 13-18, 20-25, 27-36
Y	US 4906626 (Amrein et al.) 1990-03-06	1-4, 6-11, 13-18, 20-25, 27-36
Y	Chan-Paley "Depression and senile dementia of the Alzheimer type: A role for moclobemide" *Psychopharmacology*, 1992, 106, S137-S139	1-4, 6-11, 13-18, 20-25, 27-36
Y	Amrein et al. "Moclobemide in patients with dementia and depression" *Adv. Neurol* 1999, 80, 509-519	1-4, 6-11, 13-18, 20-25, 27-36

[x] Further documents are listed in the continuation of Box C. [x] See patent family annex.

* Special categories of cited documents
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 March 2005 (04-03-2005)	29 March 2005 (29-03-2005)
Name and mailing address of the ISA/CA *Canadian Intellectual Property Office* *Place du Portage I, C114 - 1st Floor, Box PCT* *50 Victoria Street* *Gatineau, Quebec K1A 0C9* Facsimile No: 001(819)953-2476	Authorized officer Wesley Sharman (819) 934-2326

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2004/002071

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No(s).
Y	Wesnes et al. "Potential of moclobemide to improve cerebral insufficiency identified using a scopolamine model of aging and dementia" *Acta Psychiatr. Scand.* 1990, Suppl. 360, 71-72.	1-4, 6-11, 13-18, 20-25, 27-36
Y	US 5455254 (Mondadori) 1995-10-3	1-4, 6-11, 13-18, 20-25, 27-36
Y	Tolbert et al. "Selegiline in treatment of behavioural and cognitive symptoms of Alzheimer disease" *Annals of Pharmacotherapy*, 1996, 30, 1122-1129.	1, 6-8, 13-15, 20-22, 27-36
Y	CA 2022552 (Tetrud et al.) 1992-02-03	1, 6-8, 13-15, 20-22, 27-36
Y	Katz et al. "Comparison of risperidone and placebo for psychosis and behavioural disturbances associated with dementia: A randomized, double-blind trial." *J. Clin. Psychiatry*, 1999, 60(2), 107-115.	1-4, 6-11, 13-18, 20-25, 27-36
Y	De Deyn et al. "A randomized trial of risperidone, placebo and haloperidol for behavioural symptoms of dementia" *Neurology*, 1999, 53, 946-955.	1-4, 6-11, 13-18, 20-25, 27-36
Y	Schatz "Olanzapine for psychotic and behavioural disturbances in Alzheimer disease" *Annals of Pharmacotherapy*, September 2003, 37, 1321-1324.	1-4, 6-11, 13-18, 20-25, 27-36
Y	CA 2219902 (Beasley) 1996-12-05	1-4, 6-11, 13-18, 20-25, 27-36
Y	Gareri et al. "Conventional and atypical antipsychotics in the elderly" *Clin. Drug. Invest.* July 2003, 23(5), 287-322.	1-4, 6-11, 13-18, 20-25, 27-36
Y	Tariot et al. "Pharmacologic therapy for behavioural symptoms of Alzheimer's disease" *Clin. Geriatr. Med.* 2001, 17(2), 359-376.	1-4, 6-11, 13-18, 20-25, 27-36

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International application No.
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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [x] Claim Nos. : 1-7, 29 and 33

because they relate to subject matter not required to be searched by this Authority, namely :

Although claims 1-7, 29 and 33 are directed to methods of medical treatment, a search has been carried out based on the alleged effects of the combination of a monoamine oxidase inhibitor and an antipsychotic agent in the treatment of dementia.

2. [ ] Claim Nos. :

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. [ ] Claim Nos. :

because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

see Further Information sheet PCT/ISA/210

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :
4. [X] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. : 1-4, 6-11, 13-18, 20-25, 27-36

Remark on Protest [ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2004/002071

Further information continued from PCT/ISA/210:

The claims of the present international application are directed to a plurality of alleged inventions as follows:

Group A - Claims 1-4, 6-11, 13-18, 20-25 and 27-36 are directed in part towards a composition for treating dementia comprising a monoamine oxidase inhibitor in combination with an anti-psychotic agent, a method for treating dementia comprising administering a monoamine oxidase inhibitor in combination with an anti-psychotic agent and a kit for treating dementia comprising a monoamine oxidase inhibitor in combination with an anti-psychotic agent.

Group B - Claims 1-4, 6-11, 13-18, 20-25 and 27-36 are directed in part towards a composition for treating depression comprising a monoamine oxidase inhibitor in combination with an anti-psychotic agent, a method for treating depression comprising administering a monoamine oxidase inhibitor in combination with an anti-psychotic agent and a kit for treating depression comprising a monoamine oxidase inhibitor in combination with an anti-psychotic agent.

Group C - Claims 1-4, 6-11, 13-18, 20-25 and 27-36 are directed in part towards a composition for treating apathy comprising a monoamine oxidase inhibitor in combination with an anti-psychotic agent, a method for treating apathy comprising administering a monoamine oxidase inhibitor in combination with an anti-psychotic agent and a kit for treating apathy comprising a monoamine oxidase inhibitor in combination with an anti-psychotic agent.

Group D - Claims 1, 5-8, 12-15, 19-22 and 26-36 are directed in part towards a composition for treating dementia comprising a selective serotonin inhibitor in combination with an anti-psychotic agent, a method for treating dementia comprising administering a selective serotonin inhibitor in combination with an anti-psychotic agent and a kit for treating dementia comprising a selective serotonin inhibitor in combination with an anti-psychotic agent.

Group E - Claims 1, 5-8, 12-15, 19-22 and 26-36 are directed in part towards a composition for treating depression comprising a selective serotonin inhibitor in combination with an anti-psychotic agent, a method for treating depression comprising administering a selective serotonin inhibitor in combination with an anti-psychotic agent and a kit for treating depression comprising a selective serotonin inhibitor in combination with an anti-psychotic agent.

Group F - Claims 1, 5-8, 12-15, 19-22 and 26-36 are directed in part towards a composition for treating apathy comprising a selective serotonin inhibitor in combination with an anti-psychotic agent, a method for treating apathy comprising administering a selective serotonin inhibitor in combination with an anti-psychotic agent and a kit for treating apathy comprising a selective serotonin inhibitor in combination with an anti-psychotic agent.

The claims on file do not fulfill the requirements of Rule 13 (PCT).

The distinguishing features that are set forth in the claims of each group, respectively, are sufficiently different that separate searching and art evaluation is required for each group. The subject matter of each group relates toa combination therapy, either involving a combination of a monoamine oxidase inhibitor and an anti-psychotic agent (Groups A, B or C) or a combination of a selective serotonin inhibitor and an anti-psychotic agent (Groups D, E or F) for treating dementia, depression or apathy. Each combination represents a separate inventive concept in that the inventive concept in a combination must rest in the union of elements cooperating synergistically to produce a unitary result that is more than the sum of the known characteristics of the individual elements. In view of this, the combination of a monoamine oxidase inhibitor with an anti-psychotic agent involves a different inventive concept than the combination of a selective serotonin inhibitor with an anti-psychotic agent. In addition, dementia, depression and apathy are three distinct conditions. While depression and/or apathy may or may not occur in an patient suffering from dementia, depression and apathy are clearly different medical conditions as compared to dementia. Furthermore, page 8, lines 19-20 of the current description states that "Apathy is generally a behaviour disorder that is related to, but can be differentiated from, depression". Page 8, lines 27-29 also states that "Apathy refers to a syndrome closely related to major depression in that apathy is characterized by a lack of feeling or emotion or indifference. However, Apathy may be distinguished from major depression by the absence of depressed mood." while page 9, lines 5-7 states that "Diagnosing apathy in a patient requires that abulia, akinesia, akinetic mutism, depression, dementia, delirium, despair and demoralization by ruled out." Apathy is a specific neuropsychiatric syndrome that is distinct from depression and distinguishing these two syndromes has therapeutic implications. Therefore, the treatment of each of these conditions using each of the above mentioned combinations each represents a separate inventive concept.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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International application No.
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